

Inspiratory resistance delays the reporting of symptoms with central hypovolemia: association with cerebral blood flow

Caroline A. Rickards,¹ Kathy L. Ryan,¹ William H. Cooke,² Keith G. Lurie,³ and Victor A. Convertino¹

¹United States Army Institute of Surgical Research, Fort Sam Houston, Texas; ²Department of Health and Kinesiology, University of Texas at San Antonio, San Antonio, Texas; and ³Advanced Circulatory Systems, Inc., Department of Emergency Medicine at the University of Minnesota, and the Minneapolis Medical Research Foundation, Hennepin County Medical Center, Minneapolis, Minnesota

Submitted 7 February 2007; accepted in final form 13 May 2007

Rickards CA, Ryan KL, Cooke WH, Lurie KG, Convertino VA. Inspiratory resistance delays the reporting of symptoms with central hypovolemia: association with cerebral blood flow. *Am J Physiol Regul Integr Comp Physiol* 293: R243–R250, 2007. First published May 16, 2007; doi:10.1152/ajpregu.00087.2007.—We tested the hypothesis that breathing through an inspiratory threshold device (ITD) during progressive central hypovolemia would protect cerebral perfusion and attenuate the reporting of presyncopal symptoms. Eight human subjects were exposed to lower-body negative pressure (LBNP) until the presence of symptoms while breathing through either an active ITD (-7 cmH₂O impedance) or a sham ITD (0 cmH₂O). Cerebral blood flow velocity (CBFV) was measured continuously via transcranial Doppler and analyzed in both time and frequency domains. Subjects were asked to report any subjective presyncopal symptoms (e.g., dizziness, nausea) at the conclusion of each LBNP exposure. Symptoms were coincident with physiological evidence of cardiovascular collapse (e.g., hypotension, bradycardia). Breathing on the active ITD increased LBNP tolerance time (mean \pm SE) from $2,014 \pm 106$ s to $2,259 \pm 138$ s ($P = 0.006$). We compared CBFV responses at the time of symptoms during the sham ITD trial with those at the same absolute time during the active ITD trial (when there were no symptoms). While there was no difference in mean CBFV at these time points (sham, 44 ± 4 cm/s vs. active, 47 ± 4 ; $P = 0.587$), total oscillations (sum of high- and low-frequency spectral power) of CBFV were higher ($P = 0.004$) with the active ITD (45.6 ± 10.2 cm/s²) than the sham ITD (22.1 ± 5.4 cm/s²). We conclude that greater oscillations around the same absolute level of mean CBFV are induced by inspiratory resistance and may contribute to the delay in symptoms and cardiovascular collapse that accompany progressive central hypovolemia.

inspiratory threshold device; cerebral blood flow regulation; lower-body negative pressure

THE PRESERVATION OF CEREBRAL blood flow during hypotensive stress is integral in delaying the onset of presyncopal symptoms and maintaining consciousness. Recent data reported from several investigations have demonstrated the benefits of an inspiratory impedance threshold device (ITD) in elevating cerebral perfusion pressure in animals (39, 40) and reducing the reporting of presyncopal symptoms in humans (8, 27) with reductions in central blood volume.

The ITD was designed to create a greater reduction in intrathoracic pressure during inspiration, enhancing the natural vacuum within the chest (26, 37). This vacuum promotes an increase in venous return, thereby increasing ventricular pre-

load and subsequent cardiac output (Q) and arterial blood pressure (9, 26). Breathing on the ITD also increases cerebral blood flow velocity (CBFV) in resting, supine humans (12) and in the hemorrhaging porcine model, application of negative intrathoracic pressure reduces intracranial pressure (ICP) and subsequently elevates cerebral perfusion pressure (40, 41). The effect of breathing through an ITD on cerebral blood flow in spontaneously breathing humans has not been investigated under the condition of reduced central blood volume.

In this study, we used lower-body negative pressure (LBNP) as a surrogate for hemorrhage in conscious humans (13). Application of LBNP elicits reproducible responses that are physiologically similar to acute hemorrhage; the progressive decrease in central blood volume reduces venous return, ventricular preload, stroke volume (SV), Q, and arterial blood pressure and increases heart rate (HR) (7, 13). LBNP also reduces CBFV (16, 18, 43), which may lead to the reporting of subjective symptoms, such as dizziness, lightheadedness, nausea, and visual disturbances. We hypothesized that breathing on the active ITD during progressive LBNP would elevate or maintain CBFV, delay the onset of symptoms, and subsequently increase tolerance to this hypovolemic stress.

MATERIALS AND METHODS

Subjects. Eight (3 women, 5 men) healthy, normotensive, non-smoking subjects volunteered to participate in this study (age, 29 ± 2 yr; height, 174 ± 2 cm; weight, 77 ± 5 kg) conducted at the U.S. Army Institute of Surgical Research, Fort Sam Houston, TX. All experimental procedures and protocols were reviewed and approved by the Institutional Review Board of the Brooke Army Medical Center, Fort Sam Houston, TX. A complete medical history and physical examination were obtained on each of the potential subjects prior to being approved for testing. In addition, female subjects underwent a urine pregnancy test within 24 h prior to experimentation. Subjects were instructed to maintain their normal sleep pattern and refrain from exercise, alcohol, and stimulants, such as caffeine and other nonprescription drugs 24 h prior to testing to reduce their potential acute effects on cardiovascular responsiveness. During a familiarization session that preceded each experiment, subjects received a verbal briefing and a written description of all procedures and risks associated with the experiments and were made familiar with the laboratory, the protocol, and procedures. Each subject gave their written informed consent to participate in the study.

Study design. LBNP was used in the present investigation as an experimental tool to reduce central blood volume (i.e., simulate

Address for reprint requests and other correspondence: Caroline A. Rickards, U.S. Army Institute of Surgical Research, 3400 Rawley E. Chambers Ave., Bldg. 3611, Fort Sam Houston, TX 78234-6315 (e-mail: carolinerickards@hotmail.com).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

| Report Documentation Page | | | | Form Approved OMB No. 0704-0188 | |
|--|------------------------------------|-------------------------------------|--|--|---------------------------------|
| Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. | | | | | |
| 1. REPORT DATE 01 JUL 2007 | | 2. REPORT TYPE N/A | | 3. DATES COVERED - | |
| 4. TITLE AND SUBTITLE Cerebral blood flow response and its association with symptoms during orthostatic hypotension | | | | 5a. CONTRACT NUMBER | |
| | | | | 5b. GRANT NUMBER | |
| | | | | 5c. PROGRAM ELEMENT NUMBER | |
| 6. AUTHOR(S) Rickards C. A., Cohen K. D., Bergeron L. L., Burton B. L., Khatri P. J., Lee C. T., Ryan K. L., Cooke W. H., Doerr D. F., Convertino V. A., | | | | 5d. PROJECT NUMBER | |
| | | | | 5e. TASK NUMBER | |
| | | | | 5f. WORK UNIT NUMBER | |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234 | | | | 8. PERFORMING ORGANIZATION REPORT NUMBER | |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) | | | | 10. SPONSOR/MONITOR'S ACRONYM(S) | |
| | | | | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) | |
| 12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited | | | | | |
| 13. SUPPLEMENTARY NOTES | | | | | |
| 14. ABSTRACT | | | | | |
| 15. SUBJECT TERMS | | | | | |
| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT SAR | 18. NUMBER OF PAGES 8 | 19a. NAME OF RESPONSIBLE PERSON |
| a. REPORT unclassified | b. ABSTRACT unclassified | c. THIS PAGE unclassified | | | |

hemorrhage) in humans (13). With the use of a neoprene skirt designed to form an airtight seal between the subject and the chamber, the application of LBNP (below the iliac crest) results in a redistribution of blood away from the upper body (head and heart) to the abdomen and lower extremities. Thus, this model provides a unique method of investigating interventions, such as the ITD under conditions of controlled, experimentally-induced, hypovolemic hypotension.

All subjects were instrumented for the noninvasive, continuous measurement of HR via a standard ECG, and beat-to-beat arterial systolic (SBP) and diastolic (DBP) blood pressures via infrared finger plethysmography with a Finometer blood pressure monitor (TNO-TPD; Biomedical Instrumentation, Amsterdam, The Netherlands). An appropriately sized Finometer® blood pressure cuff was placed on the middle finger of the left hand, which, in turn, was laid at heart level. Resting, supine blood pressure measurements were verified against a manual sphygmomanometer recording to validate Finometer readings. The difference between these two techniques was $1.2 \pm 1.9\%$ for SBP and $6.6 \pm 1.8\%$ for DBP.

CBFV of the right middle cerebral artery (MCA) was recorded using a 2-MHz Doppler probe (EZ-Dop, DWL Elektronische Systeme, Sipplingen, Germany) positioned at a constant angle over the temporal window, located above the zygomatic arch. The transcranial Doppler (TCD) procedure for measuring CBFV has previously been described (1, 28). Briefly, the ultrasound signal emitted from the Doppler probe is reflected from erythrocytes within the MCA and back to the probe. The difference in frequency between the emitted signal and the reflected signal, the Doppler shift, is used to calculate CBFV via fast Fourier transform analysis (1, 28, 29, 31). The resultant waveform (similar to a blood pressure waveform) is produced via spectral analysis of the blood flow velocity signal (28).

Each subject underwent exposure to an LBNP protocol designed to test their tolerance to experimentally induced hypotensive hypovolemia. The LBNP protocol consisted of a 5-min controlled rest period followed by 5 min of chamber decompression at -15 , -30 , -45 , and -60 mmHg and additional increments of -10 mmHg every 5 min until the onset of cardiovascular collapse or the completion of 5 min at -100 mmHg. Cardiovascular collapse was defined by one or a combination of the following criteria: 1) a precipitous fall in SBP > 15 mmHg and/or a sudden bradycardia, 2) progressive diminution of SBP below 70 mmHg, or 3) voluntary subject termination due to the onset of subjective presyncopal symptoms such as gray-out, sweating, nausea, dizziness, or general discomfort. Each LBNP exposure represented a complete experimental session. Subjects completed three experimental sessions: 1) an initial protocol to determine LBNP tolerance without the application of any ITD, 2) during spontaneous breathing through a face mask with an ITD set at a resistance of approximately -7 cmH₂O (active ITD), and 3) during spontaneous breathing through the same face mask using an ITD with no inspiratory resistance (sham ITD). Experimental sessions were separated by a minimum of 2 wk to avoid the possibility of increased LBNP tolerance due to multiple exposures (19, 20). The ITD devices (active or sham) were placed on the subjects at one LBNP level lower than the level that produced cardiovascular collapse during the initial tolerance protocol. For example, a subject who experienced cardiovascular collapse at -60 mmHg LBNP during the initial tolerance protocol would begin breathing on the sham or active ITD at -45 mmHg during the treatment experiments. Because the initial tolerance protocol was only used to determine when to place the ITD device, these data were not used in subsequent analyses for this report. The order of the two ITD treatments was randomized so that three of the subjects underwent testing during active ITD treatment first, and five of the subjects underwent testing with the sham ITD treatment first. All experimental protocols for a given subject were initiated at the same time of day.

Experimental intervention. The ITD is a small, light-weight, disposable plastic valve that was recently developed for treatment of a

number of different clinical conditions associated with significant life-threatening hypotension (24, 26, 32, 33, 38). The ITD includes a specially designed valve that closes when the pressure within the thorax is less than atmospheric pressure and a second valve (termed the safety check valve) that opens at a preset negative intrathoracic pressure. In the spontaneously breathing subject, the ITD creates a small vacuum within the chest, drawing blood from the extrathoracic venous system into the heart each time the subject takes a breath (21, 22, 25). By increasing preload to the heart, the ITD results in an immediate increase in SBP and DBP (4, 5, 12, 21, 25) and a reduction in ICP with a subsequent increase in cerebral perfusion pressure (40) and CBFV (12). Inspiratory and expiratory pressures were recorded directly from the ITD using a commercial pressure transducer (MKS Instruments, Andover, MA) connected to the face mask, and end-tidal CO₂ was measured on a breath-by-breath basis as subjects breathed through the mask (BCI Capnograph Plus; Smiths Medical, Waukesha, WI).

Data analysis. Continuous, beat-to-beat ECG, Finometer and Doppler, and breath-to-breath end-tidal CO₂ and ITD pressure recordings were sampled at 500 Hz and recorded directly to a computer-based data acquisition software package (WinDAQ, Dataq Instruments, Akron, OH). R waves generated from the ECG signal were detected and marked at their occurrence in time. DBPs, SBPs, and diastolic and systolic flow velocities were subsequently marked from the Finometer and Doppler tracings, respectively. Using the arterial pressure waveform as an input, SV was estimated on a beat-by-beat basis using the pulse contour method outlined by Jansen et al. (17) and Q was estimated by multiplying SV by HR; mean arterial pressure (MAP) was calculated via the equation, $MAP = DBP + 1/3(SBP - DBP)$. Mean CBFV was calculated as: $mean\ CBFV = diastolic\ CBFV + 0.4(systolic\ CBFV - diastolic\ CBFV)$ from the CBFV waveform.

All time and frequency domain variables were calculated from the final 3 min of the baseline period (T1) under each ITD condition. To uncover the physiological mechanisms underlying the protective effect of ITD breathing during exposure to LBNP, the time point of cardiovascular collapse during the sham ITD trial was first identified for each subject; this time point was designated T2 (see Fig. 1). Data were then analyzed for both the sham and active ITD trials using this absolute time as the reference point. To capture the dynamic responses at cardiovascular collapse, all time domain variables were calculated from the 10 heart beats of data immediately preceding T2; the only exceptions were end-tidal CO₂ and respiratory rate, which were calculated from the final 1 min of data preceding T2, as 10 heart beats were not sufficient to accurately calculate these variables. For frequency domain variables, the final 3 min of data prior to T2 were analyzed under both ITD conditions.

Oscillatory patterns of arterial blood pressures and CBFVs were determined with fast Fourier power spectral analysis. Data were made equidistant by interpolating linearly and resampling at 5 Hz. Data were then passed through a low-pass impulse response filter with a cutoff frequency of 0.5 Hz. Three-minute data sets were fast Fourier transformed with a Hanning window to obtain power spectra. Spectral power was expressed as the integrated area within the low-frequency (LF = 0.04 to 0.15 Hz) and high-frequency (HF = 0.15 to 0.4 Hz) ranges.

We calculated the coherence among MAP and mean CBFV by dividing the cross-spectral densities of the two signals by the product of the individual autospectra. At the LF where signals are coherent (i.e., ≥ 0.5), transfer function magnitudes among MAP and mean CBFV represent a frequency dependence of dynamic cerebral autoregulation (42). The transfer function magnitude expressing the frequency relation of cerebral autoregulation was calculated by dividing the cross spectrum of MAP and mean CBFV by the autospectrum of MAP. Transfer functions were considered valid and averaged at the LF only when coherence values were ≥ 0.5 .

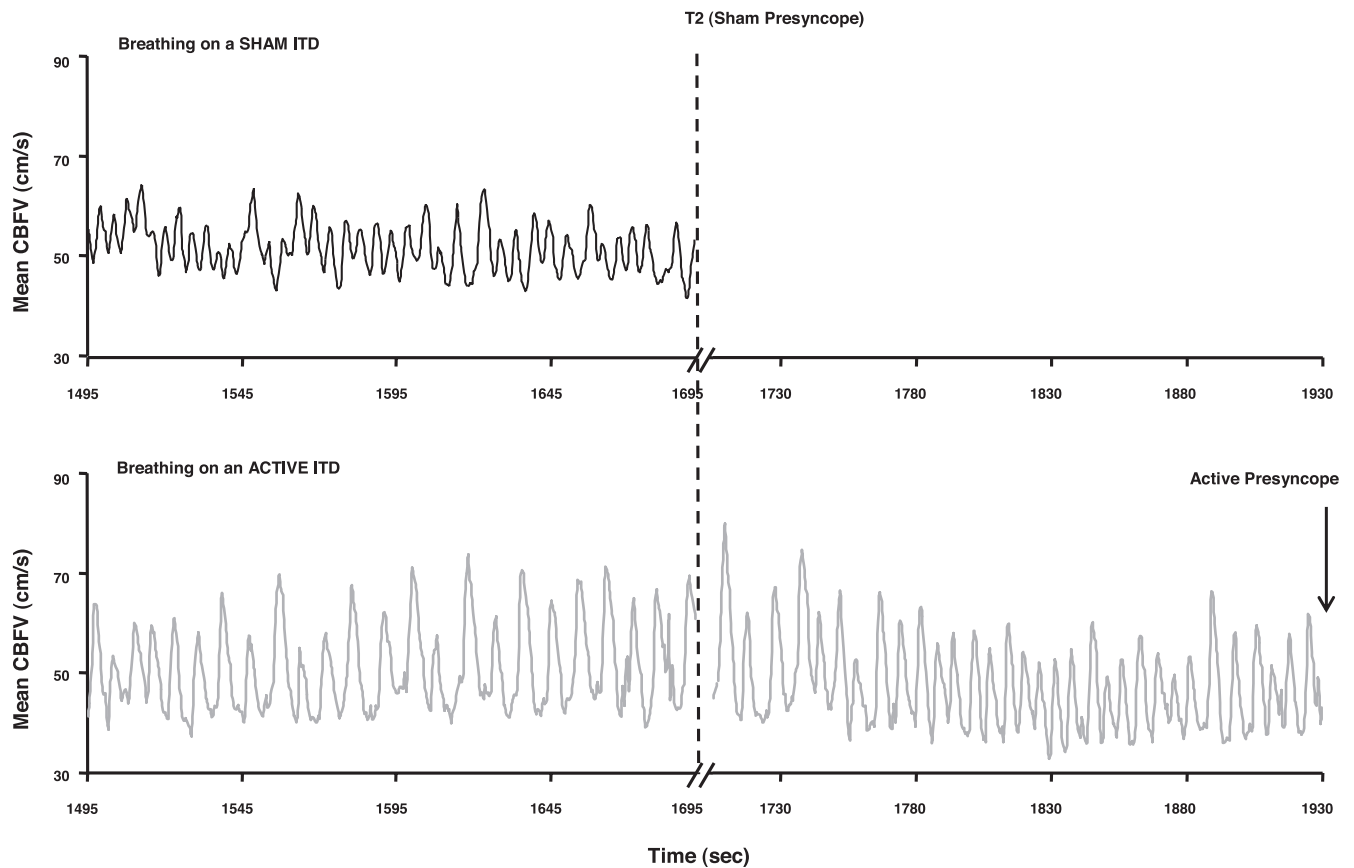


Fig. 1. A representative tracing of mean cerebral blood flow velocity (CBFV) oscillations for 1 subject at the time point of sham presyncope (T2) during the sham inspiratory threshold device (ITD) trial (*top*) and during the active ITD trial (*bottom*). In this example, all hemodynamic responses were analyzed immediately prior to T2 (1,695 s) for both trials, even though presyncope did not occur until 1,930 s during the active ITD trial. For this subject, the absolute mean CBFV at T2 for the sham ITD was 50 cm/s and 51 cm/s for the active ITD. Black line = sham ITD trial; gray line = active ITD trial.

Statistical analysis. A paired Student's *t*-test was used to compare the sham ITD and active ITD LBNP tolerance times. A two-way (time, T1 and T2; ITD condition, active and sham) analysis of variance for repeated measures was used for comparison of all physiological variables, followed by Tukey's post hoc tests. All data are presented as means \pm SE and exact *P* values are presented for all comparisons.

RESULTS

Of the 16 trials (8 active ITD, 8 sham ITD), only one subject (during the active ITD trial) completed the LBNP protocol to -100 mmHg. As previously reported (10), breathing on the sham ITD did not increase LBNP tolerance

time compared with the initial LBNP tolerance trial, indicating there was no sham effect. Breathing on the active ITD increased LBNP tolerance time from $2,014 \pm 106$ s with the sham ITD to $2,259 \pm 138$ s ($P = 0.006$). There was no difference in any of the baseline (T1) time or frequency domain variables between the active and sham ITD trials ($P \geq 0.456$) (Table 1). Figure 1 is a representative tracing of the mean CBFV response during the final 3 min of the sham ITD trial (T2) and at the same absolute time during the active ITD trial (T2).

At T2, when subjects were breathing on the sham ITD, mean CBFV had decreased by $37 \pm 5\%$ from 69 ± 4 cm/s to $44 \pm$

Table 1. Time domain data at T1 and T2 during the sham ITD and active ITD trials

| Variable | Sham ITD | | | Active ITD | | | Sham vs. Active |
|----------------------------------|----------------|----------------|----------------------------|----------------|----------------|----------------------------|----------------------------|
| | T1 | T2 | <i>P</i> Value (T1 vs. T2) | T1 | T2 | <i>P</i> Value (T1 vs. T2) | <i>P</i> Value (T2 vs. T2) |
| Systolic CBFV, cm/s | 95 \pm 4 | 71 \pm 4 | <0.001 | 99 \pm 9 | 68 \pm 5 | <0.001 | 0.690 |
| Diastolic CBFV, cm/s | 51 \pm 4 | 31 \pm 4 | <0.001 | 48 \pm 4 | 38 \pm 4 | 0.013 | 0.173 |
| Mean CBFV, cm/s | 69 \pm 4 | 44 \pm 4 | <0.001 | 68 \pm 6 | 47 \pm 4 | <0.001 | 0.587 |
| MAP, mmHg | 92 \pm 4 | 59 \pm 6 | <0.001 | 91 \pm 4 | 87 \pm 3 | 0.473 | <0.001 |
| Q, l/min | 5.3 \pm 0.3 | 3.5 \pm 0.4 | <0.001 | 5.1 \pm 0.4 | 4.5 \pm 0.3 | 0.029 | 0.002 |
| End-tidal CO ₂ , mmHg | 39.3 \pm 0.7 | 25.8 \pm 2.9 | <0.001 | 40.0 \pm 0.7 | 23.3 \pm 1.8 | <0.001 | 0.091 |
| Respiratory rate, breaths/min | 14 \pm 1 | 15 \pm 2 | 0.398 | 14 \pm 1 | 11 \pm 1 | 0.029 | 0.007 |

Values are means \pm SE; *n* = 8 subjects. T1, baseline; T2, absolute time point of presyncope during sham trial; ITD, inspiratory threshold device; CBFV, cerebral blood flow velocity; MAP, mean arterial pressure; Q, cardiac output.

4 cm/s ($P < 0.001$). At the same absolute time during the active ITD trial (when there were no symptoms), mean CBFV had fallen to a similar level of 47 ± 4 cm/s from 68 ± 6 cm/s at rest ($P < 0.001$), a drop of $30 \pm 2\%$ (Table 1). While there was no apparent difference in absolute mean CBFV between the two conditions ($P = 0.587$), analysis of cerebral oscillations identified significant effects of ITD breathing (Fig. 1). Breathing through the active ITD increased both HF and LF oscillations, and subsequently total oscillations (the sum of LF and HF power) in mean CBFV at T2 (Fig. 2A and Table 2), coincident with an absence of symptoms. This increase in total oscillatory power with active ITD breathing was more than twofold greater than at the same time during the sham ITD trial ($P = 0.004$).

Mean CBFV decreased by 37% in relative proportion to the reduction in estimated Q of 35% during the sham trial to presyncope (Fig. 3). In comparison, CBFV decreased by 30% at T2, despite only a 12% reduction in Q when subjects were breathing on the active ITD (Fig. 3). Additionally, at T2 there was no change in MAP when subjects were breathing on the active ITD ($P = 0.473$) compared with a

36% decrease from baseline ($P < 0.001$) when subjects were breathing on the sham ITD. This maintenance of MAP with active ITD breathing was associated with increases in LF and total oscillations in MAP compared with the sham trial (Fig. 2B and Table 2).

Analysis of transfer magnitudes among MAP and mean CBFV at the LF revealed an effect of active ITD breathing on dynamic cerebral autoregulation at T2 compared with T1 (T1, $0.9 \pm 0.1 \text{ cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$ vs. T2, $0.6 \pm 0.1 \text{ cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$; $P = 0.009$). However, at T2 there was no difference between the active and sham ITD trials (sham ITD, $0.7 \pm 0.1 \text{ cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$ vs. active ITD, $0.6 \pm 0.1 \text{ cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$; $P = 0.482$).

Progressive LBNP elicited reductions in end-tidal CO_2 under both the sham ($-13.4 \pm 2.9 \text{ mmHg}$, $P < 0.001$) and active ITD ($-17.9 \pm 1.9 \text{ mmHg}$, $P < 0.001$) conditions, but there was no difference between conditions (Table 1). Breathing through the active ITD elicited a decrease in respiration frequency from 14 ± 1 breaths/min at T1 to 11 ± 1 breaths/min at T2 ($P = 0.029$). This rate of breathing was lower than during the sham ITD trial ($P = 0.007$).

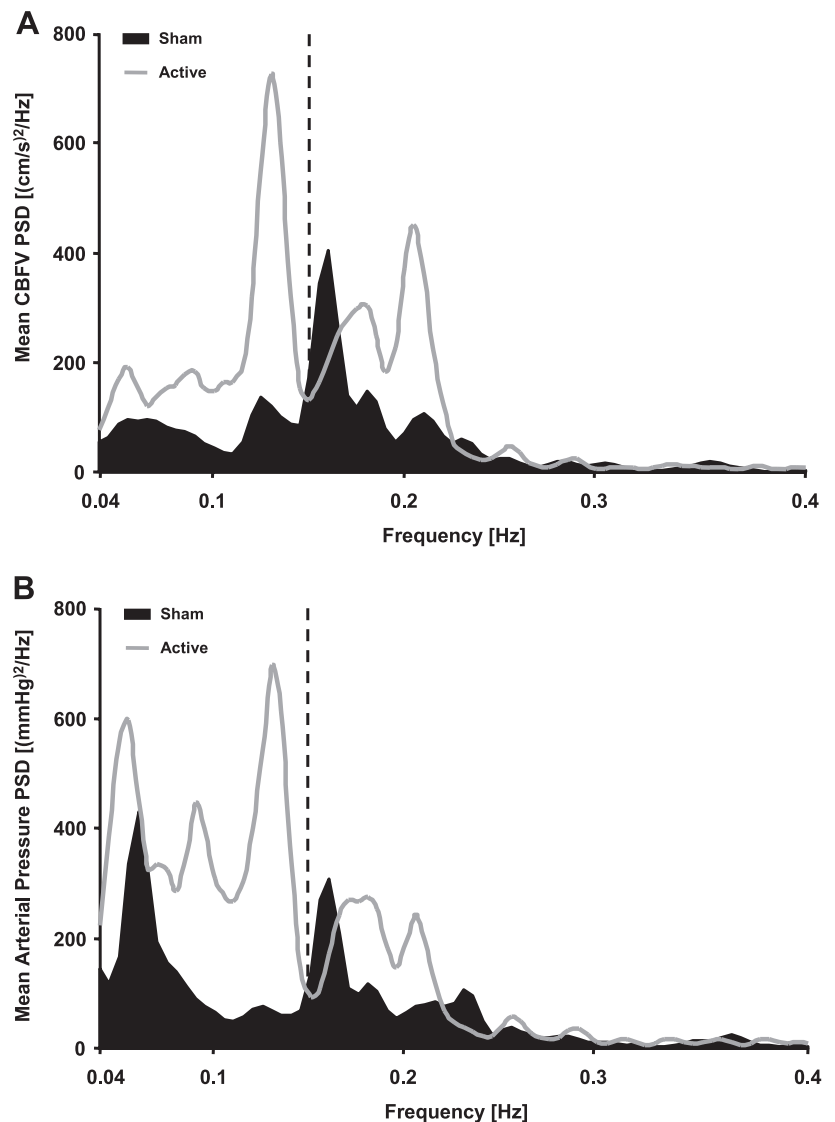


Fig. 2. Average mean CBFV (A) and mean arterial pressure (B) power spectral density (PSD) at T2 for the sham (black) and active (gray line) ITD trials. The vertical dashed line represents the separation of low-frequency (0.04–0.15 Hz) and high-frequency (0.15–0.4 Hz) spectral bands.

Table 2. Frequency domain data at T1 and T2 for the sham ITD and active ITD trials

| Variable | Sham ITD | | | Active ITD | | | Sham vs. Active |
|--|----------|----------|---------------------|------------|-----------|---------------------|---------------------|
| | T1 | T2 | P Value (T1 vs. T2) | T1 | T2 | P Value (T1 vs. T2) | P Value (T2 vs. T2) |
| Mean CBFV _{HF} , cm/s ² | 1.3±0.4 | 13.1±3.8 | 0.083 | 1.4±0.4 | 20.9±8.3 | 0.008 | 0.234 |
| Mean CBFV _{LF} , cm/s ² | 6.5±1.6 | 9.0±2.4 | 0.668 | 8.0±1.7 | 24.7±7.2 | 0.012 | 0.007 |
| Mean CBFV _{TOTAL} , cm/s ² | 7.9±1.6 | 22.1±5.4 | 0.099 | 9.5±1.9 | 45.6±10.2 | <0.001 | 0.004 |
| MAP _{HF} , cm/s ² | 1.1±0.2 | 12.3±3.0 | 0.013 | 1.2±0.3 | 17.0±4.6 | 0.001 | 0.244 |
| MAP _{LF} , cm/s ² | 6.3±1.3 | 14.2±4.7 | 0.395 | 7.7±2.1 | 41.2±12.2 | 0.003 | 0.002 |
| MAP _{TOTAL} , cm/s ² | 7.3±1.3 | 26.5±7.1 | 0.066 | 8.8±2.2 | 58.1±11.2 | <0.001 | <0.001 |
| MAP-CBFV-TF _{LF} , cm·s ⁻¹ ·mmHg ⁻¹ | 0.8±0.1 | 0.7±0.1 | 0.482 | 0.9±0.1 | 0.6±0.1 | 0.009 | 0.482 |

Values are means ± SE; *n* = 8 subjects. HF, high frequency; LF, low frequency; TF, transfer function.

DISCUSSION

We hypothesized that breathing through an active ITD during progressive central hypovolemia induced by LBNP would delay the onset of presyncopal symptoms and increase tolerance by attenuating the fall in cerebral blood flow. In partial support of our hypothesis, LBNP tolerance increased and presyncopal symptoms were delayed by ~4 min (245 s) when subjects breathed on the active ITD. Unexpectedly, however, this protective effect was not associated with the maintenance of CBFV.

Previous investigations have revealed that spontaneously breathing on the active ITD is associated with elevations in mean CBFV in passive, supine humans (12), and cerebral perfusion pressure in pigs following significant (35–50%) hemorrhage (40, 41). While subjective symptoms of presyncope cannot be ascertained with an animal model of hemorrhage, breathing on the active ITD attenuated the reporting of symptoms during the hypotensive challenge of the squat-stand test in human subjects (8), and in patients with orthostatic hypotension (27). However, neither ICP nor cerebral blood flow were recorded during these two studies to determine whether the reduction in symptoms was related to cerebral perfusion. We therefore hypothesized that the delay in presyncopal symptoms in the current study would be associated with protection of mean CBFV. Unexpectedly, mean CBFV de-

creased to the same absolute level during both the sham and active ITD trials. However, a number of factors indicate that breathing on the active ITD may have protected absolute cerebral blood flow (i.e., maintained cerebral autoregulation) during progressive central hypovolemia despite the reduction in CBFV.

Ogoh et al. (30) and Van Lieshout et al. (36) have clearly demonstrated that maintaining a higher *Q* is associated with an elevated CBFV under conditions of rest, orthostasis, and exercise. In agreement with these findings, we found a directly proportional relationship between the changes in *Q* and CBFV with progressive LBNP during the sham ITD trial. As the LBNP stimulus was, by design, exactly the same during the two ITD conditions, we expected any relative change in CBFV to be directly proportional to the relative change in *Q* at T2 while breathing on the active ITD. However, against expectations, we found that a 30% reduction in CBFV was associated with only a 12% fall in *Q*.

With the known relationship between *Q* and CBFV, this 12% reduction in *Q* while breathing on the active ITD should have elicited a fall in CBFV of ~8 cm/s. Instead, CBFV was reduced by 21 cm/s with the active ITD, more than double the predicted value. One of two possible conclusions emerges from these findings. First, an unlikely explanation is that the relative magnitude of reduction in cerebral blood flow was similar

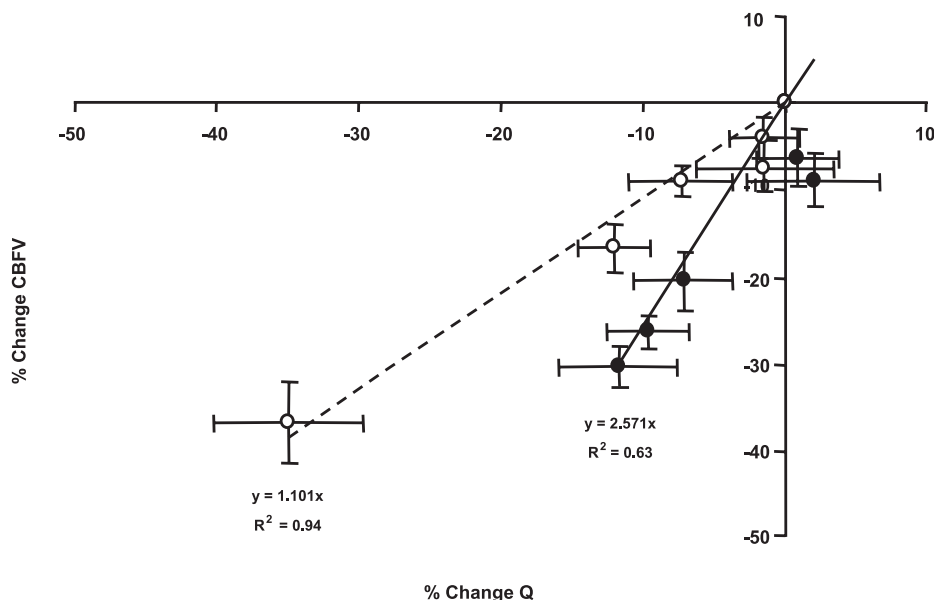


Fig. 3. The linear regression between the %change from baseline in cardiac output (*Q*) and mean CBFV during the sham ITD (white circles, dashed line) and active ITD (black circles, solid line) trials. Each point represents the group average for %change in *Q* and CBFV at 20, 40, 60, 80, and 100% of maximum tolerated lower-body negative pressure (means ± SE).

between the sham and active ITD conditions, suggesting that cerebral blood flow has no relationship with symptoms. A more likely possibility is that CBFV during active ITD breathing does not reflect the relative protection of cerebral blood flow as a result of the changing diameter of the MCA and a subsequent reduction in resistance. Although the MCA diameter does not change during LBNP alone (35), we do not know the effect of breathing through an ITD on MCA dimensions (a fundamental assumption and limitation of the measurement of cerebral blood flow by TCD). As there are data that indicate that breathing on an active ITD decreases ICP (40, 41), it is possible that a more negative ICP (the vacuum effect) could increase MCA diameter. In this scenario, breathing on the active ITD could result in higher cerebral blood flow compared with the sham ITD despite similar reductions in CBFV. Thus, the combination of reducing ICP (40, 41) and increasing perfusion pressure (40) provides a possible mechanism for the ITD to protect cerebral autoregulation and delay the onset of symptoms during progressive central hypovolemia.

Our data are the first to suggest the possibility that the measurement of CBFV and the calculated cerebrovascular resistance index may not be accurate indexes of flow or resistance under the condition of active ITD breathing. As such, the 10% increase in CBFV reported in a previous investigation conducted in our laboratory in supine, resting subjects (12) may have been an underestimation. Clearly, measures of absolute cerebral blood flow and/or cerebral vessel diameter with ITD breathing are required to confirm these hypotheses and to further elucidate the physiological mechanism underlying the protective effect of the ITD under conditions of hypovolemic stress.

During ITD breathing there are three key effects associated with central hemodynamics; a decrease in intrathoracic pressure (26), an increase in arterial pressure oscillations (Table 2), and the protection of Q (8, 9). At the cerebral level, there are similar decreases in ICP (40), and we have now presented evidence in this investigation to indicate increases in CBFV oscillations (Table 2). These similar responses in oscillations and pressure between the cerebral and cardiac compartments provide indirect evidence for the notion that cerebral blood flow may have been protected with ITD breathing in parallel with Q during progressive central hypovolemia in the present study.

CBFV oscillations were twofold greater in both the HF and LF domains with active ITD breathing. As demonstrated in the representative tracing (Fig. 1) oscillations during active ITD breathing were more regular, of greater amplitude, and peaked at higher velocities compared with the sham ITD. Although LBNP alone can elicit increases in cerebral blood flow oscillations (43), this effect was not statistically robust in the current study. However, breathing on the active ITD optimized this oscillatory pattern. Our results present the hypothesis that regular fluctuations of cerebral blood flow into higher maximum velocities with active ITD breathing may represent a protective mechanism for maintaining adequate cerebral perfusion that delays the onset of presyncopal symptoms and prolongs tolerance to LBNP. To our knowledge this is the first time that oscillations in CBFV have been potentially linked to cognitive function in the setting of progressive hypovolemia and hypotension. This mechanism may have clinical implications for the development of methods to protect patients from

hypotension, stroke, and other disorders associated with cerebral hypoperfusion.

The increase in total oscillatory power with active ITD breathing observed in the present study resulted from increases in oscillations in both the HF and LF domains (Fig. 2 and Table 2). As with R-R interval spectral power and arterial blood pressure, LF oscillations in CBFV are associated with sympathetic modulation of this vascular bed (3). In the resting, supine posture breathing through the active ITD did not elicit an increase in directly measured muscle sympathetic nerve activity (MSNA), nor was there an increase in mean CBFV_{LF} (12). Application of progressive LBNP and the reduction in central blood volume, however, does elicit increases in both MSNA (7, 15, 34) and mean CBFV_{LF} (43). Interestingly, in the current study, LBNP alone (sham ITD trial) did not increase CBFV_{LF}, but the combined effect of LBNP and active ITD breathing elevated CBFV_{LF} by 209%. It is possible that the LF oscillations in CBFV were not elevated at T2 during the sham trial as subjects had reached presyncope, which can be associated with sympathetic withdrawal (11). By comparison, at T2 during the active ITD trial, subjects had not yet reached presyncope, so sympathetic activity might still be elevated and may be reflected in an increase in LF oscillations.

As HF power is predominantly influenced by respiration (2, 3, 14), the increases in HF oscillatory power from baseline in both arterial pressure (MAP_{HF}) and CBFV (mean CBFV_{HF}) may be associated with the rhythmic decreases in intrathoracic pressure and ICP induced by breathing on the active ITD (40). Active ITD breathing reduced respiratory rate by 3 breaths/min, produced peak negative pressures of -12.2 ± 1.1 cmH₂O and prolonged time of inspiration by 30% compared with sham ITD breathing (10). While we do not have direct recordings of intrathoracic pressure, these data suggest that active ITD breathing further reduced negative intrathoracic pressure and prolonged the time at negative pressure for each breath compared with breathing on the sham ITD. Based on the findings of Yannopoulos et al., (40) where reductions in endotracheal pressure with ITD breathing were directly transmitted to ICP in the hemorrhaging swine model, we postulate that the rhythmic oscillations in CBFV in the HF domain are associated with breath-dependant oscillations in intrathoracic pressure and ICP.

Zhang et al. (43) contend that increases in the variability of arterial pressure with LBNP drive the simultaneous changes in CBFV, representing the attenuation of cerebral autoregulation. However, the maintenance of cerebral autoregulation with LBNP alone (sham ITD trial) and the improvement in cerebral autoregulation with LBNP and active ITD breathing (as indicated by a decrease in gain of the transfer function between MAP and CBFV), suggest that while both arterial blood pressure and CBFV displayed significant increases in oscillatory power, there is an independence of cerebral oscillations from arterial blood pressure oscillations. This finding is supported by Cencetti et al. (3) who demonstrated a phase delay between LF oscillations in cerebral blood flow and subsequent oscillations in arterial blood pressure during head-up tilt, suggesting that the cerebral oscillations originate in the cerebral circulation and do not result from the passive transmission of oscillations in arterial blood pressure. In contrast to the hypothesis that the increase in cerebral oscillations with central hypovolemia represents an attenuation of cerebral autoregulation,

tion which contributes to syncope (43), our results suggest that these oscillations may actually represent a protective mechanism that protects cerebral autoregulation and can act to delay the onset of syncope.

A terminal end-point during exposure to LBNP is the onset of presyncopal symptoms that often precedes cardiovascular collapse. Breathing on an inspiratory resistance device delayed the onset of symptoms with an associated increase in tolerance to progressive central hypovolemia. The mechanical effects of ITD breathing elevated both HF and LF oscillations in CBFV, and may have protected absolute cerebral blood flow. The increase in oscillatory power in both arterial blood pressure and CBFV may be associated with a protective effect against the development of hypotension and the onset of cardiovascular decompensation. The effect of ITD breathing on cerebral blood flow and vessel dimensions requires further investigation to elucidate the relationship between cognitive function, cerebral blood flow, and oscillations. Our results underscore the usefulness of enhancing the respiratory pump as an intervention for delaying the onset of circulatory shock in hemorrhaging patients.

ACKNOWLEDGMENTS

The authors thank the subjects for their time and cheerful cooperation, Gary Muniz for his engineering and technical assistance during the experiments, and Dr. John McManus for his assistance with physical examinations and medical monitoring of the subjects during the experiments.

Dr. Keith Lurie is a coinventor of the impedance threshold device, founded Advanced Circulatory Systems Inc. to develop the device, and will benefit from sale of the device. There are no other conflicts of interest.

The views expressed herein are the private views of the authors and are not to be construed as representing those of the Department of Defense or the Department of the Army.

GRANTS

This research was supported by Cooperative Research and Development Agreements between the U.S. Army Institute of Surgical Research and Advanced Circulatory Systems Inc. (CRDA No. DAMD17-02-0160), and by funding from the U.S. Army Combat Casualty Care Research Program. This research was performed while the author Caroline A. Rickards held a National Research Council Postdoctoral Research Associateship at the U.S. Army Institute of Surgical Research.

REFERENCES

1. Aaslid R. Developments and principles of transcranial Doppler. In: *Transcranial Doppler*, edited by Newell DW and Aaslid R. New York: Raven, 1992, p. 1–8.
2. Badra LJ, Cooke WH, Hoag JB, Crossman AA, Kuusela TA, Tahvanainen KUO, Eckberg DL. Respiratory modulation of human autonomic rhythms. *Am J Physiol Heart Circ Physiol* 280: H2674–H2688, 2001.
3. Cencetti S, Lagi A, Cipriani M, Fattorini L, Bandinelli G, Bernardi L. Autonomic control of the cerebral circulation during normal and impaired peripheral circulatory control. *Heart* 82: 365–372, 1999.
4. Convertino VA, Cooke WH, Lurie KG. Inspiratory resistance as a potential treatment for orthostatic intolerance and hemorrhagic shock. *Aviat Space Environ Med* 76: 319–325, 2005.
5. Convertino VA, Cooke WH, Lurie KG. Restoration of central blood volume: application of a simple concept and simple device to counteract cardiovascular instability in syncope and hemorrhage. *J Gravit Physiol* 12: P55–P60, 2005.
7. Convertino VA, Ludwig DA, Cooke WH. Stroke volume and sympathetic responses to lower-body negative pressure reveal new insight into circulatory shock in humans. *Auton Neurosci* 111: 127–134, 2004.
8. Convertino VA, Ratliff DA, Crissey J, Doerr DF, Idris AH, Lurie KG. Effects of inspiratory impedance on hemodynamic responses to a squat-stand test in human volunteers: implications for treatment of orthostatic hypotension. *Eur J Appl Physiol* 94: 392–399, 2005.
9. Convertino VA, Ratliff DA, Ryan KL, Doerr DF, Ludwig DA, Muniz GW, Britton DL, Clah SD, Fernald KB, Ruiz AF, Lurie KG, Idris AH. Hemodynamics associated with breathing through an inspiratory impedance threshold device in human volunteers. *Crit Care Med* 32, Suppl 9: S381–S386, 2004.
10. Convertino VA, Ryan KL, Rickards CA, Cooke WH, Metzger A, Holcomb JB, Adams BD, Lurie KG. Inspiratory resistance maintains arterial pressure during central hypovolemia: implications for treatment of patients with severe hemorrhage. *Crit Care Med* 35: 1145–1152, 2007.
11. Cooke WH, Convertino VA. Association between vasovagal hypotension and low sympathetic neural activity during presyncope. *Clin Auton Res* 12: 483–486, 2002.
12. Cooke WH, Lurie KG, Rohrer MJ, Convertino VA. Human autonomic and cerebrovascular responses to inspiratory impedance. *J Trauma* 60: 1275–1283, 2006.
13. Cooke WH, Ryan KL, Convertino VA. Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. *J Appl Physiol* 96: 1249–1261, 2004.
14. deBoer RW, Karemaker JM, Strackee J. Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. *Am J Physiol Heart Circ Physiol* 253: H680–H689, 1987.
15. Fu Q, Witkowski S, Levine BD. Vasoconstrictor reserve and sympathetic neural control of orthostasis. *Circulation* 110: 2931–2937, 2004.
16. Giller CA, Levine BD, Meyer Y, Buckley JC, Lane LD, Borchers DJ. The cerebral hemodynamics of normotensive hypovolemia during lower-body negative pressure. *J Neurosurg* 76: 961–966, 1992.
17. Jansen JR, Wesseling KH, Settels JJ, Schreuder JJ. Continuous cardiac output monitoring by pulse contour during cardiac surgery. *Eur Heart J* 11, Suppl I: 26–32, 1990.
18. Levine BD, Giller CA, Lane LD, Buckley JC, Blomqvist CG. Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. *Circulation* 90: 298–306, 1994.
19. Lightfoot JT, Febles S, Fortney SM. Adaptation to repeated presyncopal lower body negative pressure exposures. *Aviat Space Environ Med* 60: 17–22, 1989.
20. Lightfoot JT, Hilton F Jr, Fortney SM. Repeatability and protocol comparability of presyncopal symptom limited lower body negative pressure exposures. *Aviat Space Environ Med* 62: 19–25, 1991.
21. Lurie KG, Voelckel W, Plaisance P, Zielinski T, McKnite S, Kor D, Sukhum P. Use of an inspiratory impedance threshold valve during cardiopulmonary resuscitation: a progress report. *Resuscitation* 44: 219–230, 2000.
22. Lurie KG, Voelckel WG, Zielinski T, McKnite S, Lindstrom P, Peterson C, Wenzel V, Lindner KH, Samniah N, Benditt D. Improving standard cardiopulmonary resuscitation with an inspiratory impedance threshold valve in a porcine model of cardiac arrest. *Anesth Analg* 93: 649–655, 2001.
24. Lurie KG, Zielinski T, McKnite S, Aufderheide T, Voelckel W. Use of an inspiratory impedance valve improves neurologically intact survival in a porcine model of ventricular fibrillation. *Circulation* 105: 124–129, 2002.
25. Lurie KG, Zielinski T, McKnite S, Sukhum P. Improving the efficiency of cardiopulmonary resuscitation with an inspiratory impedance threshold valve. *Crit Care Med* 28: N207–N209, 2000.
26. Lurie KG, Zielinski TM, McKnite SH, Idris AH, Yannopoulos D, Raedler CM, Sigurdsson G, Benditt D, Voelckel WG. Treatment of hypotension in pigs with an inspiratory impedance threshold device: a feasibility study. *Crit Care Med* 32: 1555–1562, 2004.
27. Melby DP, Lu F, Sakaguchi S, Zook M, Benditt DG. Increased impedance to inspiration ameliorates hemodynamic changes associated with movement to upright posture in orthostatic hypotension: a randomized blinded pilot study. *Heart Rhythm* 4: 128–135, 2007.
28. Novak P, Novak V, Low PA, Petty GW. Transcranial Doppler evaluation in disorders of reduced orthostatic tolerance. In: *Clinical Autonomic Disorders*, edited by Low PA. Philadelphia, PA: Lippincott-Raven, 1997, p. 349–368.
29. Novak V, Novak P, Spies JM, Low PA. Autoregulation of cerebral blood flow in orthostatic hypotension. *Stroke* 29: 104–111, 1998.
30. Ogoh S, Brothers RM, Barnes Q, Eubank WL, Hawkins MN, Purkayastha S, O-Yurvati A, Raven PB. The effect of changes in cardiac output on middle cerebral artery mean blood velocity at rest and during exercise. *J Physiol* 569: 697–704, 2005.

31. Petty GW, Wiebers DO, Meissner I. Transcranial Doppler ultrasonography: clinical applications in cerebrovascular disease. *Mayo Clin Proc* 65: 1350–1364, 1990.
32. Plaisance P, Lurie KG, Payen D. Inspiratory impedance during active compression-decompression cardiopulmonary resuscitation. a randomized evaluation of patients in cardiac arrest. *Circulation* 101: 989–994, 2000.
33. Plaisance P, Lurie KG, Vicaut E, Martin D, Gueugniaud PY, Petit JL, Payen D. Evaluation of an impedance threshold device in patients receiving active compression-decompression cardiopulmonary resuscitation for out of hospital cardiac arrest. *Resuscitation* 61: 265–271, 2004.
34. Rea RF, Hamdan M, Clary MP, Randels MJ, Dayton PJ, Strauss RG. Comparison of muscle sympathetic responses to hemorrhage and lower body negative pressure in humans. *J Appl Physiol* 70: 1401–1405, 1991.
35. Serrador JM, Picot PA, Rutt BK, Shoemaker JK, Bondar RL. MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* 31: 1672–1678, 2000.
36. Van Lieshout JJ, Pott F, Madsen PL, van Goudoever J, Secher NH. Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. *Stroke* 32: 1546–1551, 2001.
37. Voelckel W, Lurie K, Zielinski T. Effects of active compression-decompression cardiopulmonary resuscitation with the inspiratory threshold valve in a young porcine model of cardiac arrest. *Pediatr Res* 51: 523–527, 2002.
38. Wolcke BB, Mauer DK, Schoefmann MF, Teichmann H, Provo TA, Lindner KH, Dick WF, Aeppli D, Lurie KG. Comparison of standard cardiopulmonary resuscitation versus the combination of active compression-decompression cardiopulmonary resuscitation and an inspiratory impedance threshold device for out-of-hospital cardiac arrest. *Circulation* 108: 2201–2205, 2003.
39. Yannopoulos D, McKnite S, Aufderheide TP, Sigurdsson G, Pirrallo RG, Benditt D, Lurie KG. Effects of incomplete chest wall decompression during cardiopulmonary resuscitation on coronary and cerebral perfusion pressures in a porcine model of cardiac arrest. *Resuscitation* 64: 363–372, 2005.
40. Yannopoulos D, McKnite SH, Lurie KG. Intrathoracic pressure regulation for intracranial pressure management in normovolemic and hypovolemic pigs. *Crit Care Med* 34, Suppl 12: S495–S500, 2006.
41. Yannopoulos D, Metzger A, McKnite S, Nadkarni V, Aufderheide TP, Idris A, Dries D, Benditt DG, Lurie KG. Intrathoracic pressure regulation improves vital organ perfusion pressures in normovolemic and hypovolemic pigs. *Resuscitation* 70: 445–453, 2006.
42. Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol Heart Circ Physiol* 274: H233–H241, 1998.
43. Zhang R, Zuckerman JH, Levine BD. Deterioration of cerebral autoregulation during orthostatic stress: insights from the frequency domain. *J Appl Physiol* 85: 1113–1122, 1998.

